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Updates on the Treatment of Essential Hypertension: A Summary of AHRQ's Comparative Effectiveness Review of Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Direct Renin Inhibitors

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Updates on the Treatment of Essential Hypertension: A Summary of AHRQ's Comparative Effectiveness Review of Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Direct Renin Inhibitors

Benjamin Powers, MD, MHS; Laurence Greene, PhD; and Lisa M. Balfe, MPH

Target Audiences

This CME activity is designed to meet the educational needs of physicians, pharmacists, nurses, and case managers.

Learning Objectives

Based on the findings from AHRQ's systematic review of research on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and direct renin inhibitors for treating essential hypertension in adults:

1. Compare the effectiveness of the therapy options for controlling blood pressure and reducing risks of cardiovascular mortality and morbidity
2. Describe key differences in side-effect profiles, tolerability, and adherence/persistence outcomes associated with the therapy options
3. Summarize conclusions regarding the comparative benefits and risks of the therapy options on prespecified subpopulations of patients

Funding

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DISCLOSURES

Benjamin Powers produced this program under contract with PRIME Education, Inc. and reports no financial or other conflicts of interest related to the subjects in this report. Laurence Greene and Lisa Balfe are employees of PRIME Education, Inc., a medical education company that receives grants and funding for educational programs from various pharmaceutical manufacturers. Donna Chiefari, Pat Gleason, Karen Gunning, Kathleen Jarvis, Steven Kayser, Joyce Knestrick, and Mori Krantz reported no financial interests or other relationships with companies with commercial interests in antihypertensive medications or other potential conflicts of interest related to the subjects in this report. Diana Brixner reported a consulting relationship with Novartis Pharmaceuticals.

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Updates on the Treatment of Essential Hypertension: A Summary of AHRQ's Comparative Effectiveness Review of Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Direct Renin Inhibitors

Benjamin Powers, MD, MHS; Laurence Greene, PhD; and Lisa M. Balfe, MPH

ABSTRACT

BACKGROUND: In 2007, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review (CER) on the benefits and risks of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) for treating essential hypertension in adults. The main findings indicated that the 2 classes of antihypertensive medications caused similar reductions in blood pressure, although higher rates of adverse events, especially cough, were reported by patients treated with ACEIs. In addition, the 2007 review indicated no treatment-related differences in lipid levels, glycemic control, or progression of kidney disease among the agents. Since 2007, 39 relevant studies have been published that compare outcomes for adults treated with ACEIs versus ARBs or a drug in one of these 2 classes versus a direct renin inhibitor (DRI). To systematically analyze findings from the new research, AHRQ commissioned and, in June 2011, published an updated comparative effectiveness review on the benefits and risks of agents that target the renin-angiotensin-aldosterone system (RAAS), specifically ACEIs, ARBs, and DRIs.

OBJECTIVES: To (a) familiarize health care professionals with the methods and findings from AHRQ's 2011 comparative effectiveness review on ACEIs, ARBs, and DRIs for adults with essential hypertension; (b) provide commentary and encourage consideration of the clinical and managed care applications of the review findings; and (c) identify limitations to the existing research on the benefits and risks of ACEIs, ARBs, and DRIs.

SUMMARY: Consistent with the findings from AHRQ's 2007 report, the 2011 update indicated no overall differences in blood pressure control, mortality rates, and major cardiovascular events in patients treated with ACEIs versus ARBs. With a low strength of evidence, 2 studies reported a small significantly greater blood pressure reduction for patients treated with the DRI aliskiren versus the ACEI ramipril. Studies evaluating the DRI aliskiren versus ACEIs and ARBs on mortality and morbidity outcomes were relatively short, and few deaths or cardiovascular events occurred, resulting in insufficient evidence to discern differences. A random-effects meta-analysis of 23 RCTs comparing ACEIs and ARBs found no significant difference in the proportion of patients who achieved successful blood pressure control on a single antihypertensive agent. Compared with ARBs and the DRI aliskiren, ACEIs were consistently associated with higher rates of cough. Withdrawals due to adverse events were modestly more frequent for patients receiving ACEI rather than ARBs or DRIs; this is consistent with the differential rates of cough. There was no evidence of differential effects of ACEIs, ARBs, or DRIs on the outcomes of lipids, renal outcomes, carbohydrate metabolism or diabetes, or left ventricular mass; however, there was not a high strength of evidence for any of these outcomes. Regarding the question of whether ACEIs, ARBs, or DRIs are associated with better outcomes in specific patient subgroups, the evidence was insufficient to reach firm conclusions.

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Hypertension affects approximately 65 million individuals in the United States and is the primary attributable risk factor for mortality.[1,2] Given its damaging effects to the heart, arteries, brain, eyes, and kidneys, hypertension is also a major cause of morbidity. Prevalent hypertension is defined as systolic blood pressure of at least 140 mm Hg and diastolic blood pressure of at least 90 mm Hg.[3-5] According to the Seventh Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, readings below these levels indicate hypertension control.[5]

Despite the widespread impact of hypertension and its negative outcomes, blood pressure control remains suboptimal. Approximately 25% of adults who have hypertension are unaware of their condition, and more than 40% of patients receiving treatment do not achieve the modest goal of < 140 mm Hg/90 mm Hg.[1,6] The main classes of antihypertensive medications are thiazide-type diuretics, calcium channel blockers, beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). Agents in the latter 2 classes target the renin-angiotensin-aldosterone-system (RAAS), which plays a significant role in regulating blood volume, arterial pressure, and cardiac and vascular function. ACEIs and ARBs are the second and fifth most commonly prescribed treatments for hypertension.[7] RAAS-targeted therapies also include direct renin inhibitors (DRIs).[8]

The 3 categories of agents within the RAAS inhibitor class are intended ultimately to inhibit the hypertensive effects of angiotensin II, which acts directly on the resistance vessels to increase systemic vascular resistance and arterial pressure. In addition, angiotensin II increases blood pressure by stimulating the adrenal cortex to release aldosterone, which causes sodium and water reabsorption as well as potassium excretion, and by promoting the secretion of antidiuretic hormone, which also leads to fluid retention. DRIs block the conversion of angiotensinogen to angiotensin I; ACEIs block the conversion of angiotensin I to angiotensin II; and ARBs selectively inhibit angiotensin II from activating the angiotensin specific receptor (AT1).

Whereas the 3 classes RAAS therapies all inhibit the effects of angiotensin II, differences in their pharmacologic effects may underlie variations in their efficacy and risks. For example, because angiotensin II can be formed through enzymes that are not affected by ACEIs, agents in this class do not block

angiotensin II production completely. Unlike ARBs and DRIs, ACEIs are associated with cough. However, ACEIs have the unique advantage of increasing levels of bradykinin, which can reduce blood pressure through its vasodilatory effects. ACEIs and ARBs cause compensatory increases in plasma renin activity, which does not occur with DRIs.[8] Despite the fact that RAAS-targeted therapies effectively lower blood pressure,[9,10] these and other differences in their mechanisms of action and effects underscore the need for research on their comparative benefits and risks.

In 2007, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review (CER) on the benefits and risks of ACEIs and ARBs for treating essential hypertension in adults.[11] The main findings indicated that the 2 classes of antihypertensive medications caused similar reductions in blood pressure, although higher rates of adverse events were reported by patients treated with ACEIs. In addition, the 2007 review indicated no treatment-related differences in lipid levels, glycemic control, or progression of kidney disease. In 2009, an analysis conducted by the Southern California Evidence-Based Practice Center indicated the need for an updated comparative effectiveness review of research on RAAS therapies.[12] The update was deemed necessary due to the publication of a significant number of new studies comparing ACEIs versus ARBs, as well as the introduction of a DRI (aliskiren) to the market. Based on this needs assessment, AHRQ commissioned and, in June 2011, published an update on the comparative effectiveness of ACEIs, ARBs, and DRIs. The systemic literature review and meta-analyses were conducted by investigators at the Duke Evidence-Based Practice Center (EPC) in Durham, North Carolina. A full technical report of the review is available on AHRQ's Effective Health Care Program website.[13]

This article summarizes the key methods and findings of the 2011 updated comparative effectiveness review on ACEIs, ARBs, and DRIs. This summary is intended to provide evidence to guide clinicians, health care payers, and policy makers in reaching decisions about appropriate therapeutic regimens for patients with essential hypertension. In addition, readers are encouraged to reflect on the potential clinical and managed care applications of the review findings.

Key Questions

For the 2011 update, the Duke EPC investigators sought to answer the following key clinical questions:

1. For adult patients (aged 18 years and older) with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?
2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?
3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

Focusing on ACEIs and ARBs only, these questions were originally developed for the 2007 AHRQ review with input from technical experts and the Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program. The questions were posted to a public website, soliciting commentary and suggestions for revision. After reviewing the public commentary, the SRC drafted final key questions and submitted them to AHRQ for approval. For the 2011 review, in response to input from the project's technical expert panel, the original key questions were modified to include the comparative risks and benefits of DRIs. The modified questions were then posted to a public website for comment and were subsequently revised and approved.

Systematic Review Methods

This section summarizes the methods by which the updated comparative review effectiveness review was conducted. Complete details about the methods are provided in the full technical report.[13]

Literature Search and Study Selection

The EPC investigators identified studies targeting the RAAS through searches of comprehensive databases of biomedical literature, including MEDLINE, EMBASE, and a register of systematic reviews in the Cochrane Hypertension Review Group. These database searches—which included systematic reviews, randomized controlled trials, and nonrandomized comparative studies—covered periods from database inception through December 2010. In addition, the EPC investigators searched for literature through reference lists of relevant review articles, regulatory agencies (e.g., U.S. Food and Drug Administration [FDA], Health Canada, and Authorized Medicines for EU), clinical trial registries, and conference publications. Abstracts were screened to select only relevant studies that made direct head-to-head comparisons of ACEIs versus ARBs, ACEIs versus DRIs, or ARBs versus DRIs. Studies in which protocols permitted adding antihypertensive therapies (if blood pressure targets were not reached) were also included if the additions were the same across treatment groups. Moreover, the literature review and selection were restricted to studies that:

1. Included adults aged 18 years or older who had essential

TABLE 1 Number of Studies (Number of Publications) Comparing ACEIs, ARBs, and DRIs[a]

		ARBs								DRI	
		Unspecified "ARBs"	Candesartan cilexetil	Eprosartan	Irbesartan	Losartan	Olmesartan medoxomil	Telmisartan	Valsartan	Aliskiren	Totals
ACEIs	Unspecified "ACEIs"	21 (24)	0	0	2 (2)	1 (1)	0	0	0	0	24 (27)
	Benazepril	0	0	0	0	0	0	0	1 (1)	0	1 (1)
	Captopril	0	0	0	0	2 (2)	0	0	0	0	2 (2)
	Enalapril	0	4 (4)	2 (6)	4 (4)	14 (15)	0	5 (5)	2 (2)	0	31 (36)
	Fosinopril	0	0	0	2 (2)	1 (1)	0	0	0	0	3 (3)
	Lisinopril	0	6 (6)	0	0	1 (1)	0	3 (3)	5 (5)	0	15 (15)
	Perindopril	0	1 (1)	0	0	3 (3)	0	3 (3)	0	0	7 (7)
	Quinapril	0	0	0	2 (2)	3 (3)	0	0	0	0	5 (5)
	Ramipril	0	0	0	0	2 (2)	1 (1)	5 (5)	3 (3)	2 (3)	13 (14)
	Trandolapril	0	0	0	0	1 (1)	0	0	0	0	1 (1)
DRI	Aliskiren	0	0	0	0	1 (1)	0	0	0	—	1 (1)
	Totals	21 (24)	11 (11)	2 (6)	10 (10)	29 (30)	0	16 (16)	11 (11)	2 (3)	—

[a]*Source: Table 4 in Sanders, GD, et al. AHRQ comparative effectiveness report number 34 (June 13, 2011);[13] there were no studies or publications for moexipril. Totals exceed 100 studies (110 publications) because some trials reported more than 1 ACEI versus ARB treatment comparison.*

ACEI = angiotensin-converting enzyme inhibitor; AHRQ = Agency for Healthcare Research and Quality; ARB = angiotensin receptor blocker; DRI = direct renin inhibitor.

hypertension
2. Included at least 24 patients
3. Followed patients for at least 12 weeks
4. Reported at least 1 prespecified outcome of interest

From an original search yielding 2,090 citations, 1,083 were excluded at the abstract screening stage. From the remaining 1,007 studies, 110 articles that reported direct treatment comparisons (based on 100 separate studies) met the inclusion criteria and were abstracted into evidence tables. The 100 studies included 74 randomized controlled trials (RCTs), 4 nonrandomized controlled trials, 16 retrospective cohort studies, 3 prospective cohort studies, 1 cross-sectional cohort study, 1 case-control study, and 1 retrospective chart review. Study follow-up time ranged from 12 weeks to approximately 70 months; however, 61% of the studies included in the review lasted 26 weeks or less. The EPC investigators identified 36 new studies (published since the 2007 review) that compared ACEIs versus ARBs. Three new studies that met inclusion criteria compared an ACEI or ARB to a DRI.

Treatment Comparisons and Outcomes of Interest

Table 1 shows the ACEIs and ARBs that were directly compared in the studies that met inclusion criteria and were selected for the AHRQ review. All 3 DRI studies compared an ACEI (ramipril) or ARB (losartan) with the DRI aliskiren. In addition to comparisons of a single ACEI versus a single ARB or DRI, the EPC investigators included grouped comparisons. For example, studies were included that compared (a) a specific ARB versus unspecified ACEIs, (b) unspecified ARBs versus unspecified ACEIs, and (c) an ACEI plus another antihypertensive drug in a different class (e.g., enalapril plus hydrochlorothiazide) versus an ARB plus the same drug (e.g., losartan plus hydrochlorothiazide).

For key question 1, analyses were based on the following primary outcomes:

- Blood pressure, assessed preferably with seated trough measures
- All-cause, cardiovascular-specific, or cerebrovascular-specific mortality
- Morbidity, especially myocardial infarction and stroke
- Rate of use of a single antihypertensive medication in successful blood pressure control
- Quality of life, as assessed through various standard instruments

Secondary outcomes for key question 1 were:

- Lipid levels (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol, and triglycerides)
- Rates of progression to type 2 diabetes
- Markers of carbohydrate metabolism and diabetes control (hemoglobin A1c, dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of glucose)
- Measures of left ventricular mass/function (left ventricular mass index and ejection fraction).
- Measures of kidney disease (creatinine/glomerular filtration rate, proteinuria)

For key question 2, primary analyses were based on withdrawals due to the following: adverse events; the specific adverse events of dizziness, headaches, angioedema and cough; and treatment persistence or adherence.

TABLE 2 Overview of Key Findings and Strength of Evidence[a]

	ACEIs Versus ARBs	DRI Versus ACEIs	DRI Versus ARBs
Key Question 1: Comparative Benefits			
Blood pressure control	ND ••	Favors DRI •	ND •
Mortality and major cardiovascular events	ND •	IE	IE
Quality of life	ND •	NE	NE
Rate of use of a single antihypertensive agent	ND ••	NE	NE
Risk factor reduction (lipid levels, markers of carbohydrate metabolism, diabetes control)	ND ••	NE	NE
Key Question 2: Comparative Risks			
Cough	Favors ARBs •••	IE	NE
Withdrawal due to adverse events	Favors ARBs •••	ND •	NE
Angioedema	IE	IE	IE
Therapy adherence	ND ••	IE	IE
Therapy persistence[b]	Favors ARBs ••	NE	NE

Symbol legend: • = low strength of evidence, •• = moderate strength of evidence, ••• = high strength of evidence.

[a]*Sanders, GD, et al. AHRQ comparative effectiveness report number 34 (June 2011): http://www.effectivehealthcare.ahrq.gov/ehc/products/164/696/CER-34-ACEIs-ARBs_Final-Report_20110613.pdf.*[13]

[b]*Table A in the full AHRQ report number 34 includes the conclusion that "rates of continuation with therapy appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify."*[13]

ACEI = angiotensin-converting enzyme inhibitor; AHRQ = Agency for Healthcare Research and Quality; ARB = angiotensin receptor blocker; DRI = direct renin inhibitor; IE = insufficient evidence; ND = no difference; NE = not evaluated (due to insufficient or lack of evidence).

Evaluations of Study Quality and Strength of Evidence

For each set of analyses focused on a given outcome, the investigators assessed the strength of study evidence using criteria designated in AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[14] These criteria are based on guidelines of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group.[15] The strength of evidence was assessed by the number, size, design, and quality of the studies included in a given analysis. In addition, the investigators considered risk of bias, directness, precision, consistency across studies of the same and different designs, magnitude of effect, applicability, and the potential for publication bias. The evidence was graded as *high, moderate, low, or insufficient*. The first three of these grades indicate the investigators' confidence in the extent to which the evidence reflects true, or systematic, treatment effects. A grade of *insufficient* indicates that evidence either does not exist or does not permit estimation of effects.

Comparative Benefits of RAAS Therapies

This section presents the findings that address key question 1, which focuses on the comparative benefits of ACEIs, ARBs, and DRIs. A general overview of the findings is provided in Table 2.

Blood Pressure Control

The EPC investigators concluded that ACEIs and ARBs have similar overall effects on blood pressure reduction in patients with essential hypertension. This conclusion was based on 77 studies (n = 26,170 participants) that met inclusion criteria: 70 of these studies were RCTs; 5 were nonrandomized controlled trials; 1 was a retrospective cohort study; and 1 was a case-control study. The ages of study participants ranged from means of 33 to 73 years (median age 55.4 years). The duration of patient follow-up ranged from 12 weeks to 5 years (median 24 weeks). Across the studies, initial values for mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) ranged from 127 to 199 mm Hg and 67 to 119 mm Hg, respectively (mean initial blood pressure 156/97 mm Hg).

Of the 77 studies comparing ACEIs versus ARBs for blood pressure reduction, 57 (74%) reported no significant difference between treatment classes,[16-77] 2 reported a significant advantage for ACEIs,[78-80] and 11 reported a significant advantage for ARBs (note: in some cases, results from a given study were reported in more than 1 article).[81-91] The strength of evidence derived from these studies was graded *high*. The EPC investigators did not identify any specific agent within its class that was associated with greater or lesser reduction in blood pressure. Due to substantial heterogeneity in study methods, the investigators did not conduct meta-analyses for this outcome. A noteworthy factor limiting the AHRQ review of treatment-related differences in blood pressure control is that the protocols for dose escalation and adding antihypertensive agents differed considerably across studies.

Three RCTs were identified that compared aliskiren to either an ACEI or an ARB.[92-95] Two of the studies (n = 842 and n = 901) compared ramipril with aliskiren.[92-95] The third study (n = 465) compared losartan with aliskiren.[94] Compared with the ACEI ramipril, aliskiren reduced blood pressure to a greater extent, with the absolute differences in systolic/diastolic reduction of –2.7/–1.6 mm Hg ($P = 0.006$)[92,95] and –2.3/–1.5 mm Hg ($P = 0.02$).[93] The study comparing aliskiren with the ARB losartan found no significant difference in blood pressure reduction (1.0/0.1 mm Hg, $P = 0.81$).[94] In spite of the reported differences in blood pressure reduction, these comparisons are based on limited data and should be interpreted with caution due to the overall low strength of evidence comparing DRIs with ACEIs or ARBs.

Mortality, Major Cardiovascular Events, and Quality of Life

Addressing mortality and major cardiovascular events, the EPC investigators identified 21 studies that reported outcomes of

patient deaths, myocardial infarction (MI), or stroke. Ranging in duration from 12 weeks to 5 years, the studies included 38,589 participants who received an ACEI, an ARB, or a DRI. Most of the studies excluded patients with significant cardiovascular disease and did not follow patients long enough to adequately assess mortality and cardiovascular morbidity outcomes. In the 3 studies on aliskiren, only 1 death occurred.[92-95] In the studies comparing ACEIs with ARBs, only 38 deaths and 13 strokes were reported. Thus, due to the relatively healthy patient population and short follow-up in these studies, no firm conclusions about the comparative effects of RAAS therapies on mortality and major cardiovascular events can be reached. As summarized in the full technical report of the AHRQ review, a study conducted by Barnett et al. (2004) evaluated cardiovascular outcomes in 250 patients with type 2 diabetes treated with enalapril 20 mg daily or telmisartan 80 mg daily over a 5-year period.[96] The higher-risk sample in this study included individuals with comorbidities including type 2 diabetes and early nephropathy. Among patients treated with enalapril versus telmisartan, respectively, there were similar numbers of deaths (6 in each group), strokes (6 in each group), and nonfatal MIs (6 in the enalapril group and 9 in the telmisartan group).

Four RCTs (n = 1,182) were identified that compared ACEIs to ARBs for effects on quality of life; no study evaluated this outcome for comparisons involving a DRI. In all of the studies comparing ACEIs and ARBs, no significant effects on quality of life were reported.[87,97-103]

Rate of Use of a Single Antihypertensive Agent

The EPC investigators identified 23 RCTs in which rates of successful ACEI and ARB monotherapy were evaluated. Definitions of "successful" outcomes varied across the studies, which generally used specified cutoff values for blood pressure or instances of patients who remained on a single ACEI or a single ARB throughout a study. Rates of use of a single antihypertensive agent ranged from 6% to 93% (median 55%). Using the individual study data, the EPC investigators calculated odds ratios (OR) expressed as the proportion of patients with successful blood pressure control on a single ARB versus a single ACEI. Based on a random-effects model, meta-analysis of the 23 RCTs, treatment with an ARB was associated with a nonsignificant OR of 1.08 (95% confidence interval [CI] = 0.94-1.25, $P = 0.28$) for successful monotherapy. The strength of study evidence was rated *high*.[18-20,23-24,36-40,44,47,51-52,56-57,62-63,65,75,77-78,82,84,104-106]

The rate of successful blood pressure control on a single medication is generally influenced by its efficacy as well as its tolerability and adherence. Because these outcomes may vary across studies with different designs, the EPC investigators conducted separate meta-analyses for the 3 observational studies.[75,104,106] This meta-analysis indicated a nonsignificant trend favoring ARBs for successful blood pressure control (OR = 1.258, 95% CI = 0.984-1.610, $P = 0.067$). While the magnitude of relative increase in successful monotherapy with ARBs represents a clinically important difference, this result should be interpreted with caution. The lack of concordance between pooled results in RCTs and observational studies suggests selection bias and residual confounding as potential explanations for this observed difference, rather than the inherent efficacy of the medication.

Lipid Levels and Markers of Carbohydrate Metabolism/Diabetes Control

Twenty studies reporting changes in serum lipid levels among patients treated with ACEIs versus ARBs were included in the AHRQ review; no study evaluated this outcome in comparisons involving a DRI. Study periods ranged from 3 to 24 months, which the reviewers deemed a sufficient time length to detect measurable treatment-related changes in lipid profiles. In 12 of the studies, there were no significant within-group changes in triglycerides or in total, LDL, or HDL cholesterol. In the studies that reported significant treatment-group differences in lipid changes, no consistent pattern was evident to inform a reliable conclusion for guiding treatment decisions.

Twenty-three studies in the review evaluated changes in blood glucose levels or A1c among patients treated with ACEIs versus ARBs. Conclusions are limited because none of the studies sufficiently controlled for patients' variations in diabetes medications. There were no differences in achieved glucose and A1c levels between the ACEI and ARB groups. As in the analysis for lipid changes, no consistent pattern was evident for studies reporting significant treatment-group differences in markers of carbohydrate metabolism and diabetes control.

Left Ventricular Mass/Function

The ARHQ review indicated that therapies targeting RAAS generally have beneficial effects on some measures of left ventricular mass and function; however, for the most part, the effects do not differ across treatments in the RAAS class. Measures of left ventricular (LV) mass and/or function were reported in 13 studies that met inclusion criteria. Outcomes were assessed either by LV mass index (LVMI), LV ejection fraction (LVEF), both of the previous 2 measures, or LV posterior wall thickness. Most of the studies evaluating LVMI reported significant benefits of ACEIs, ARBs, and aliskiren (i.e., reduction in LVMI).[21,23,55,60-61,64,68-69,75,77,94,99,107] However, with the exception of 1 study,[55] no differences in LVMI between treatment groups were observed. In the exception, a 6-month RCT comparing losartan with enalapril, LVMI reduction was significantly greater in the ARB (24.7%) versus ACEI (11.2%) arm ($P = 0.026$).[55] For LVEF, no studies reported significant changes among patients treated with ACEIs or ARBs. In 1 study that evaluated changes in LV posterior wall thickness, irbesartan and quinapril were both associated with significantly reduced

measures; however, no difference between the 2 therapies was observed.[64] It is noteworthy that the majority of the studies evaluating changes in LV mass and systolic function were relatively short, lasting between 6 to 12 months. This duration may not be long enough to detect treatment-related changes and differences in some measures of LV mass and systolic function.

Renal Function

RAAS agents generally have beneficial effects on some measures of renal function and proteinuria.[5] In 31 studies included in the AHRQ review, renal outcomes were measured by creatinine or glomerular filtration rate (GFR). An analysis of the 8 studies reporting post-treatment serum creatinine in ACEI and ARB treated patients gave an estimated standardized mean difference of 0.11 (95% CI = −0.054-0.272), suggesting that mean post-treatment creatinine levels are slightly higher for the ARB studies, but the difference is not statistically significant.

Analyses of changes in urinary protein and albumin excretion consistently revealed no differential effects of ACEIs versus ARBs. No differences in renal outcomes were observed in studies comparing aliskiren with an ACEI or an ARB.[93,95]

Comparative Risks of RAAS Therapies

This section summarizes the main findings of the AHRQ review pertaining to key question 2. Forty-eight studies included in the review reported rates of at least 1 specific adverse event. The EPC investigators based their main comparative analyses on withdrawals due to adverse events and risks of angioedema, dizziness, headaches, and cough. In addition, key question 2 included the outcomes of treatment adherence and persistence. An overall summary of the findings is presented in Table 2.

Withdrawals Due to Adverse Events

The AHRQ review included 41 studies comparing withdrawal rates due to adverse events among patients treated with ACEIs, ARBs, or aliskiren. In 36 studies, withdrawal rates were lower in the ARB arms (mean 3%) than the ACEI arms (mean 5%). A random-effects meta-analysis of 36 RCTs yielded an estimated OR of 0.56 (95% CI = 0.45-0.70, $P < 0.001$), indicating the odds of withdrawal due to adverse events was 44% lower among patients treated with ARBs versus ACEIs.[17-19,21-23,26,28-31,38-39,42-47,56,58,60,66,70,75,77,80-83,85,86,88,90,92-94,102,107] Meta-analysis of 2 studies comparing aliskiren with ramipril yielded a nonsignificant odds ratio of 0.89 (95% CI = 0.46-1.71).[92-93,95]

Angioedema

Angioedema has been reported to occur more frequently in patients treated with ACEIs versus ARBs.[108] However, only 4 studies reporting this adverse outcome met the inclusion criteria for the AHRQ review.[42,47,92,102] One case of angioedema was reported for a patient treated with aliskiren;[92] 4 cases were

Clinical Commentary 1: Separating the "Wheat" from the "Chaff" in Assessing Clinical Outcomes in the RAAS Category of Drugs for Essential Hypertension

When consulted about starting antihypertensive therapies in patients without compelling indications for specific antihypertensive therapy, pharmacists may select from a variety of agents. The AHRQ comparative effectiveness review update in June 2011 focuses on 3 categories of agents that manipulate the RAAS. Despite the addition of 39 studies since the previous AHRQ comparative effectiveness review in 2007, many questions remain unanswered, most frequently because of a lack of long-term studies that evaluate outcomes that matter to patients including quality of life, adherence, tolerability, adverse cardiovascular events, and mortality.

Information on blood pressure control, the surrogate outcome for improved cardiovascular health, is, however, available. For blood pressure lowering, there is sufficient evidence to confirm that ACEIs and ARBs have similar long-term effects and are thus interchangeable. The next question is to compare these agents to DRIs. The AHRQ review indicated, with limited evidence on DRI agents, that blood pressure control may be improved compared with ACEIs (2 studies) and similar to that seen with ARBs (1 study). This finding may lead some clinicians to prescribe these agents for their perceived improved efficacy. However, this should *not* be the case because a statistically significant improvement in blood pressure control is not always a clinically significant one, as demonstrated by the small differences in actual blood pressure reduction of 1.0-2.7/0.1-1.6 mm Hg for aliskiren versus ARBs and ACEIs. This magnitude of difference in blood pressure reduction would *not* be considered clinically significant to most clinicians and resembles the change that might be seen if different automated blood pressure devices or different clinicians measured the same patient's blood pressure.

Given the higher cost of DRIs over generic ACEIs and the increasing availability of generic ARBs, in addition to the minimal difference in efficacy and with insufficient long-term outcomes data, it is difficult to determine from the evidence currently available the subgroup of patients that may benefit from this pharmacologically intriguing drug class. The AHRQ comparative effectiveness review concludes with several key clinical questions that need to be addressed in the future with all of the agents in this group. Answers to these critical questions may provide clinicians with more useful data regarding the outcomes that patients really care about (the "wheat"—quality of life, tolerability, and reduction in morbidity and mortality), as opposed to the currently available clinically insignificant differences in blood pressure reduction (the "chaff" of the RAAS class of drugs).

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reported for patients treated with lisinopril;[42,47] and 1 case of "severe disabling Quincke's angioneurotic edema" was reported for a patient treated with enalapril.[102] In these studies, no cases of angioedema were reported for patients treated with candesartan[42] or telmisartan.[47,102] Due to the insufficient evidence, conclusions about the comparative risks of angioedema in patients treated with RAAS therapies were precluded.

Dizziness, Headaches, and Cough

As reported in 31 and 30 studies, respectively, rates of dizziness and headache ranged from 1% to approximately 20% among patients treated with ACEIs, ARBs, or DRIs. Based on similar mean rates of dizziness and headache across treatment groups, the EPC investigators concluded that there were no significant differential effects of RAAS therapies on these outcomes. Treatment-related differences were most apparent for cough. In all 40 studies that evaluated cough in patients treated with ACEIs versus ARBs, rates were higher in the ACEI arms; however, the magnitude of difference was small in some of the studies.[16-18,20,23,26,28-31,38-40,42-43,45-47,56,58-59,66,74,77-78,80,82-85,88-91,102,109-113] The mean cough rates for ARBs and ACEIs were 2.2% and 8.7%, respectively, or an absolute difference of 6.5%. A random-effects meta-analysis of the 40 studies yielded an estimated OR of 0.23 (95% CI = 0.18-0.29, $P < 0.001$), indicating that the risk of cough in relative terms is 77% lower for ARB-treated patients versus ACEI-treated patients.

Two studies reported the average cough rates for the ACEI ramipril versus the DRI aliskiren (9.5% vs. 4.1%, and 13.3% vs.

Clinical Commentary 2: The Payer Perspective on ACEIs, ARBs, and DRIs for Treating Essential Hypertension

In making formulary decisions about antihypertensives targeting the RAAS, it is important to balance clinical effectiveness and cost. Effectiveness can be measured by the difference in blood pressure lowering, decreasing major cardiovascular (CV) events, and reducing mortality rates. Cost considerations include the availability of generic drugs in some classes versus only branded agents in others. To date, the evaluation of these characteristics has most commonly led to a preferred position for ACEIs on a formulary. The ACEI category has relatively strong evidence of benefits for key outcomes, delivered at the lowest cost driven by many generic options. The positioning for ARB therapy recognizes the possibility of decreased efficacy of ACEI therapy due to the so-called ACE-escape (unblocked angiotensin II over time) and lower tolerability caused by cough. The current AHRQ update has considered additional evidence published since the 2007 AHRQ report on drugs that act on the renin system in comparing ACEIs and ARBs and has evaluated the relatively new category of DRIs for the treatment of hypertension.

Overall, the 2011 update to the 2007 AHRQ report offers little new evidence to assist in further evaluation of DRIs versus the already available ACEIs and ARBs for formulary inclusion. The key outcomes of blood pressure control, CV event rate, and mortality are often the most important factors to consider when making formulary decisions. There is reasonable evidence of long-term reductions in blood pressure control for ARBs and ACEIs. However, limited evidence exists on long-term control of blood pressure for DRIs versus either of these 2 categories; 2 studies found small reductions in blood pressure for aliskiren versus ACEIs, and 1 study found no difference in blood pressure reduction for aliskiren versus an ARB. However, there is an overall low strength of evidence in comparing DRIs with ACEIs or ARBs in blood pressure reduction.

For endpoint outcomes, the AHRQ review is consistent with the findings from the large adequately powered prospective randomized controlled trial (ONTARGET) that compared an ACEI with an ARB, finding no difference in CV event rates. Despite significant evidence of decreased mortality and CV events with ACEIs, cost/outcome differences between ACEIs and ARBs are difficult to interpret due to low event rates. Whereas 18 studies included in the AHRQ review investigated the comparative effectiveness of ACEIs versus ARBs for outcomes of mortality and CV events, only 3 studies compared the DRI aliskiren with an ACEI or an ARB, hindering any type of cost/outcome analysis for the RAAS class as a whole.

The side effect with the greatest differentiation between ACEIs and ARBs is cough, with reported rates of 1.2% to 7.8% across RCTs and retrospective studies. This evidence may correlate to lower withdrawal rates (2.3% absolute rate in RCTs) and a potential for improved persistency. In the 2 studies that looked at DRIs, the reduction in cough versus ACEIs was greater for the ARBs than DRIs, and withdrawal rates were comparable. Thus, improved persistency for DRIs versus ACEIs would not be expected.

The available evidence is considerable to support either ACEIs or ARBs as single-agent therapy for essential hypertension, but there is no comparable evidence for the DRIs. There are no substantial outcome differences in metabolic indicators between ACEIs or ARBs and no evidence for DRIs. Long-term evidence on quality of life is lacking for any of the drugs.

Overall, the evidence summarized above applies across all patients, due to insufficient evidence for any subgroups. The June 2011 update to the 2007 AHRQ report supports the continued formulary positioning of ACEIs as a first-line therapy in the RAAS class, with ARBs providing an alternative option for those who do not respond or experience cough as a side effect. Review of the supplemental DRI evidence published since the 2007 report provides no support for this category other than as a therapy option in hypertensive treatments that target the renin system. Formulary access could consider the DRIs as a therapeutic option versus the ARBs following therapeutic failure with an ACEI. A more restricted position could consider DRI use as third-line therapy after failure with an ACEI and an ARB. In the absence of evidence of differences in comparative effectiveness, these decisions will most likely be driven by cost, including discount contracting with brand-name manufacturers and generic availability. ACEIs are widely available in generic form, and at least 3 ARBs become available generically in 2012, in addition to losartan that has been available generically since April 2010.

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4.2%, respectively).[92,93] In a meta-analysis of these studies, the estimated OR was 0.33 (95% CI = 0.22-0.49), indicating the risk of cough is 67% lower for aliskiren-treated patients versus ramipril-treated patients.

Therapy Persistence and Adherence

The EPC investigators identified 39 studies that reported data on therapy persistence or adherence. Persistence, reported in 4 RCTs and 13 longitudinal cohort studies, was assessed by whether patients remained on their initial RAAS therapy throughout a study. In the studies included in the AHRQ review, adherence was usually assessed by the number of prescribed pills that patients took, expressed relative to 100%. With the exception of 1 study in which the mean adherence rate was higher for patients treated with ARBs versus ACEIs,[66] there were no treatment-related differences in adherence. The rates of adherence to ACEIs and ARBs were high, exceeding 90% in all studies. In most studies that evaluated therapy persistence, continuation rates were slightly higher for ARBs versus ACEIs.

RAAS Therapies Outcomes in Patient Subgroups

The third key question guiding the AHRQ comparative effectiveness review focused on the benefits and risks of RAAS therapies in subgroups of patients categorized by age, race, ethnicity, sex, comorbidities, and concurrent use of other medications. For these analyses, the study evidence was generally insufficient to reach firm conclusions about whether ACEIs, ARBs, or DRIs are more effective, associated with fewer adverse events, or better tolerated in specific patient subgroups.

In 3 of 4 studies that involved separate analyses of blood pressure outcomes in women, no differences in efficacy were observed between ACEIs and ARBs.[33,37,86] However, in the largest of the 4 studies (n = 286), blood pressure was reduced significantly more among women treated with candesartan compared with enalapril.[87] The mean between-group difference was 5.5/2.2 mm Hg ($P < 0.01$).[87] Three of 4 studies that analyzed outcomes for black patients revealed no treatment-group differences in blood pressure reduction.[45,78,86] The fourth study reported a greater reduction in diastolic blood pressure among black patients treated with losartan versus enalapril.[56]

In 5 of 8 studies that involved separate analyses for older adults (aged 65 years or older), no differences in blood pressure reduction were observed between the ACEI and ARB arms.[20,24,37,86,113] The other 3 studies reported a significant benefit of ARBs compared with ACEIs in older patients.[56,82,84] In a study of patients aged 65 years or older, blood pressure was lowered –2.3/–1.5 mm Hg in the aliskiren group compared with the ramipril group.[93]

Due to the limited availability of data on mortality, MI, and stroke, the evidence was insufficient to reach conclusions regarding these outcomes in different patient subgroups treated with ACEIs, ARBs, or DRIs. Furthermore, the evidence is insufficient to derive conclusions about whether certain patient subgroups are more likely to have adverse effects associated with specific RAAS therapies. Regarding the outcome of persistence to therapy, the evidence was generally insufficient to determine whether certain patient subgroups are more or less likely to continue taking an ACEI or an ARB. However, the EPC investigators observed several trends suggesting subgroup-specific predictors of persistence. The highest levels of persistence are generally observed among older adults and patients with a history of cardiovascular disease.

Conclusions and Directions for Future Research

As summarized earlier, the 2007 AHRQ-supported comparative effectiveness review on ACEIs and ARBs for adults with essential hypertension found similar outcomes for blood pressure control, higher rates of cough in patients treated with ACEIs, and no treatment-related differences in changes in lipid levels, glycemic control, or renal function. Moreover, in the 2007 review, the evidence was generally insufficient to reach conclusions regarding differential effects of ACEIs and ARBs on long-term clinical outcomes and in patient subgroups. Although numerous direct comparison studies have been published since 2007, the June 2011 update summarized in this article indicates few new findings regarding the comparative benefits and risks of ACEIs and ARBs. In addition, due to insufficient evidence, no firm conclusions can be reached about the comparative effectiveness of DRIs. With the exception of the determination of insufficient evidence to assess the comparative effectiveness of DRIs, the conclusions from the 2007 report did not change substantially in the updated review.[13]

As detailed by the EPC investigators in the AHRQ full technical report in June 2011, a number of methodological shortcomings are inherent in the studies from which the evidence was derived.[13] Limitations in study design, small sample sizes, lack of sufficient patient follow-up, and procedural flaws compromised the quality and applicability of some of the findings. In suggesting directions for future research, the EPC investigators call for new comparative effectiveness studies with pragmatic designs that assess long-term clinical outcomes. In addition, new studies are needed with broader representations of patient subgroups (e.g., older adults and racial minorities) and analyses of patients with essential hypertension and various comorbid conditions. To address unanswered questions about antihypertensive medications, the investigators suggest evaluations of therapies within classes and long-term studies comparing outcomes in patients treated with DRIs versus ACEIs and ARBs.

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